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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/806,842	11/13/2001	Eliezer Masliah	6627-PA9013	7702
25225	7590	11/15/2005	EXAMINER	
MORRISON & FOERSTER LLP 12531 HIGH BLUFF DRIVE SUITE 100 SAN DIEGO, CA 92130-2040			STANDLEY, STEVEN H	
			ART UNIT	PAPER NUMBER
			1649	

DATE MAILED: 11/15/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/806,842	MASLIAH ET AL.	
	Examiner	Art Unit	
	Steven H. Standley	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 25 August 2005.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 16,17,21-25,27 and 28 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 16,17,21-25,27 and 28 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413) |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | Paper No(s)/Mail Date. _____ |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152) |
| Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/25/05 has been entered.

Claims 16-17, 21-25, and 27-28 are under examination.

Withdrawn Rejections

Claim Rejections - 35 USC § 112

2. The rejection of claims 16-17, 21-25, and 27-28 under 35 USC § 112, 1st paragraph, new matter, is withdrawn due to applicant's amendments. Accordingly, the priority date of the instant application is considered by the examiner to be October 6, 1999.
3. The rejection of claim 17 under 35 USC § 112, 1st paragraph, written description, is withdrawn due to applicant's amendment.
4. The rejection of claims 16-17, 21-25, and 27-28 under 35 USC § 112, 1st paragraph, enablement, is withdrawn due to applicant's amendment.
5. The rejection of claims 16-17, 21-25, and 28 under 35 USC § 112, 1st paragraph, enablement, is withdrawn due to applicant's amendment.

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6. The rejection of claim 17 under 35 USC § 112, 2nd paragraph as indefinite is withdrawn due to applicant's amendment.

Claim Rejections - 35 USC § 102

7. The rejection of claim 16-17 under 35 USC § 102(b) as anticipated by Jensen et al is withdrawn due to applicant's amendment.

8. The rejection of claim 16, 21-22 and 27-28 under 35 USC § 102(a) and (e) as anticipated by Wolozin, US patent number 6,780,971, is withdrawn due to applicant's amendment.

Claim Rejections - 35 USC § 103

9. The rejection of claims 16, 21, and 24-23 under 35 USC § 103 as anticipated by Beire et al, US patent number 6,184, 351, is withdrawn because the presence of iron in the cell as a pro-oxidant is established below.

10. The rejection of claims 21-23 under 35 USC § 103 as anticipated by Hashimoto et al is withdrawn due to applicant's amendment.

Rejections Maintained or Necessitated

Claim Objections

11. Claims 16 is objected to because of the following informalities: Claim 16 contains reference to 'NACP,' without first disclosing the meaning of the acronyms in

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the claims. In order to make the description of the invention more clear, the first claim that mentions these acronyms should fully express the phrase, and be followed by parentheses, which identify the acronym to be used in the following claim(s). Appropriate correction is required.

Claim Rejections - 35 USC § 112

5. The rejection of claims 16-17, 21-25, and 28 under 35 USC § 112, 1st paragraph, enablement, is maintained for the reasons made of record in the prior office action. Applicant is advised that cancellation of claim 27 (as it points out that the first pair of samples are necessarily from different sources) would obviate the rejection. Applicant is also advised that the samples of claim 16 could be construed as either from the same source or different sources.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claim 25 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 25 is a dependent claim but applicant has deleted from which claim it depends. Therefore it is indefinite.

Claim Rejections - 35 USC § 102

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

13. Claims 16, 21-25, and 27 are rejected under 35 USC 102(e) as being anticipated by Biere et al, US patent 6184351, filed 9/24/99.

Biere et al provides an in vitro aggregation assay which can be used to identify synuclein aggregation inhibitors. The method of Biere et al teaches exposure to a potential nucleation-affecting agent (see claim 4). Biere et al also provides for transgenic mice expressing synuclein (see example 6, Beire et al) and in vivo methods of screening compounds analogous to those described for the in vitro methods (see example 6) that ameliorate the pathological conditions underlying Parkinson's (see abstract) which are identified as aggregation of synuclein to form Lewy bodies in striatal dopaminergic neurons (meeting the limitations of claims 22-23; Column 1, background). Furthermore, in the case of E. coli expression of synuclein and transgenic animal expression of synuclein, the expressed synuclein proteins are exposed to ferric and ferrous iron as evidenced by Korge et al, and Bauminger et al (see literature cited but not relied upon). Therefore, aggregation is inherently nucleated by Ferric or Ferrous iron. For instance, see Korge et al (page 420, right column) wherein they disclose that "There is now ample evidence to suggest that the availability and binding of transition metals, most importantly iron ions, to biomoleclues is a major determinant in the generation of highly reactive oxygen species that initiate oxidative damage. Although

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the cellular level of free iron is under tight control, a small pool of iron moving among transferrin, cytoplasm, mitochondria, and ferritin is always present." Thus, synuclein in a cell is inherently exposed to oxidizing iron and aggregated. See Lutz (abstract only; cited but not relied upon) who discloses that hydrogen peroxide is formed endogenously.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

14. Claims 16-17, 24-25, and 27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jensen et al (1997) as evidenced by Harris et al (1995) and further in view of Jenner et al, (Sept., 1998).

Jensen et al, as disclosed in prior office actions, teaches the identification of agents (small peptides) that inhibit aggregation of A-beta and synuclein fragments and indicates such inhibitors might be used as substances for the construction of drugs. Thus, Jensen et al. teach a method for identification of molecules that inhibit aggregation of A-beta and synucleins. Jensen et al., teach a method for inducing aggregation of amyloidogenic proteins, see in particular Experimental, pp 540, column 2, lines 24-44, and Results, Abeta binding to alpha- and beta synuclein, pp. 541-542,

figures 1-3. Treatments include incubation or exposure to Abeta, NAC, SDS, or beta-synuclein (and in some cases inhibition of aggregation). Jensen is silent as to Abeta or synuclein being subjected to a metal ion oxidative condition. However, Harris et al teach direct evidence of oxidative injury produced by beta amyloid peptide. Thus, as evidence by Harris the contact of A-beta with NACP taught by Jensen is equivalent to exposure to an oxidative condition which is noted to provide aggregation.

Thus, Jensen et al teach "a method for identifying an inhibitor" the steps of inducing protein aggregation in a first sample comprising NACP/alpha synuclein by exposing the first sample to a treatment, inducing protein aggregation in a second sample and comparing the aggregation level of NACP/alpha-synuclein in the second sample wherein less aggregation in the first sample is indicative of an inhibitor of aggregation.

Jensen et al does not teach using ferric or ferrous iron as a means of oxidizing the polypeptides to induce aggregation.

Jenner et al. teaches the aggregates formed in lewy bodies (which contain synuclein in both Parkinson's disease and Alzheimer's disease) are directly related to oxidation by iron. Jenner et al further teach that "postmortem analysis [of patients with Parkinson's] shows increased levels of iron [in the brain; abstract, Jenner et al]," and that "the inability of the substantia nigra to handle damaged or mutant (eg, alpha-synuclein) proteins may lead to their aggregation and deposition and to the formation of Lewy bodies [abstract]." Further in relation to iron as a catalyst for oxidative damage

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resulting in aggregation, Jenner et al disclose "However, H₂O₂ can react with iron to form the highly reactive and cytotoxic hydroxyl radical (OH) via the Fenton reaction [S73, left col]." Jenner et al. state "Iron is a pro-oxidant that can donate an electron to enhance redox reactions through its conversion from ferrous (Fe²⁺) to ferric (Fe³⁺) form. In this way it can catalyze the formation of ROS...[s73, right col]."

Therefore it would have been obvious to one of ordinary skill to combine the teachings of Jensen et al with Jenner et al and use iron to induce oxidation of synuclein via instead of A-beta. The motivation to combine is given by Jenner et al, who state that "iron is a pro-oxidant [S73, right column]," and "postmortem analysis [of parkinson's patients] shows increased levels of iron," and "the inability of the substantia nigra to handle [oxidatively] damaged...synuclein proteins may lead to their aggregation [abstract]."

15. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Korge et al disclose that intracellular iron in a cell acts as an oxidant. Bauminger et al disclose that e. coli possess intracellular iron as well. Lutz et al disclose that hydrogen peroxide is an endogenous molecule.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Steven Standley whose telephone number is **(571) 272-3432**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 5:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres can be reached on **(571) 272-0867**.

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The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

Steve Standley, Ph.D.

11/7/05



LORRAINE SPECTOR
PRIMARY EXAMINER